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1. Untranslatable words are replaced with asterisks (***).
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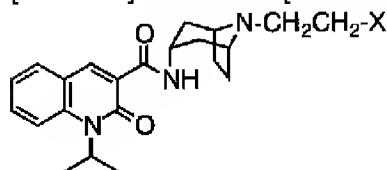
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CLAIM + DETAILED DESCRIPTION

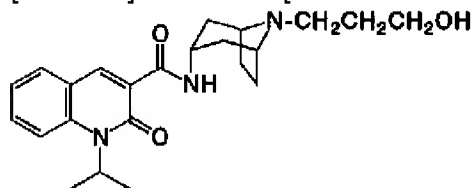
[Claim(s)]

[Claim 1]A formula [Chemical formula 1]



(X express a hydroxymethyl group, a methoxy group, an ethoxy group, or a morpholino group among a formula.) -- a digestive system disease treating agent using a compound expressed or a salt permitted in physic as an active principle.

[Claim 2]A formula [Chemical formula 2]



The digestive system disease treating agent coming out and using the compound expressed or the salt permitted in physic as an active principle.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]This invention relates to the enterokinesis functional improvement agent based on a serotonin 4 receptor-stimulation operation in more detail about a digestive system disease treating agent.

[0002]

[Description of the Prior Art]Serotonine has very variegated physiology activity with the neurotransmitter which exists widely in the living body. A serotonin receptor is added to three subtypes, the serotonin 1 from the former, the serotonin 2, and the serotonin 3, Existence of serotonin 4 acceptor was reported by 1988 Dumuis A and others (the 34th volume of Molecular Pharmacology, the 880th page, 1988).

[0003]Conjugate [of the serotonin 4 acceptor] is carried out to guanine nucleotide joint protein, and it promotes adenylate-cyclase (adenylatecyclase) activity. By the nerve, promoting isolation of acetylcholine is suggested by existing in synapse anterior part and intercepting K channel to a cyclic (cyclic)AMP dependency.

[0004]In a central nervous system, to striatum, a hippocampus, substantia nigra, tuberculum olfactorium, etc., and it is few to a cerebral cortex. In addition, the report which shows a relaxation operation of a smooth muscle and the operation to the cardiovascular system in Homo sapiens and a swine is made.

[0005]In the alimentary canal, various operations are accepted and potentiation of a contraction reaction and guinea pig intestinum-ileum electrical stimulation contraction, an derivation operation of CI secretion of the rat distance colon, etc. through the cholinergic nerve in the guinea pig intestinum ileum and the proximal colon are reported.

[0006]These results have the intervention of serotonin 4 acceptor which exists in an alimentary canal in derivation and maintenance of an alimentary canal peristaltic movement, the serotonin 4 receptor-stimulation agent carried out activation of the lowered gastrointestinal tract motor function, and it has suggested having the therapy and improving action of an intestinal disease and symptoms accompanying motor disorder.

[0007]Cisapride, RENZAPURIDO, etc. which have a serotonin 4 receptor-stimulation operation by promotion of movement of a gastrointestinal tract actually Chronic gastritis, Postoperative stomach motility, such as diabetes mellitus and gastric resection, the heartburn accompanying a stomach excretory function fall, anorexia, It shall be effective for the therapy of an improvement of digestive symptoms, such as epigastralgia and abdomen enlarged feeling of, and esophagitis regurgitica, pseudoileus, constipation, etc. (the 6th volume of Alimentary Pharmacology and Therapeutics, the 273rd page, 1992).

[0008]As a heterocyclic compound which has the antagonism or the stimulation of a serotonin receptor, the quinoline derivative which has the antagonism of serotonin 3 acceptor is indicated by JP,H4-226980,A. It uses for inhibition of the nausea and the emesis induced at the time of anticancer drug administration and radiation irradiation, and also since serotonin 3 receptor antagonist shows the movement depressant action of a lower digestive tract to an alimentary canal, the indication in a had diarrhea type hypersensitivity disease is considered. On the other hand, the quinazoline carboxylic acid derivative is indicated by JP,H3-197462,A

as a heterocyclic compound effective in the therapy of digestive trouble etc. Although clinical use of the pirenzepine is carried out as anti-secretion and a antiulcer drug in the alimentary canal field as muscarine 1 receptor antagonist, Since the muscarinic receptor which exists in a smooth muscle is the muscarine 2 (or muscarine 3), this takes into consideration that the depressant action to the enterokinesis is minor.

[0009]However, it does not say that muscarine 1 receptor antagonist does not act on the enterokinesis at all in an in vitro (In vitro) examination, but minor depressant action is shown. Muscarine 1 acceptor exists in an intramural ganglion in an alimentary canal, and this is considered to be because it to participate in neural transmission promotion.

[0010]Therefore, with serotonin 4 receptor-stimulation medicine, revealing a functional promotion operation over the range where an alimentary canal is wide is expected to serotonin 3 receptor antagonist and muscarine 1 receptor antagonist being considered to be the drugs which expected the drug effect based on functional depressant action.

[0011]As described above, the report is not made about the quinoline compound which has antagonism or the stimulation outstanding to serotonin 4 acceptor.

[0012]

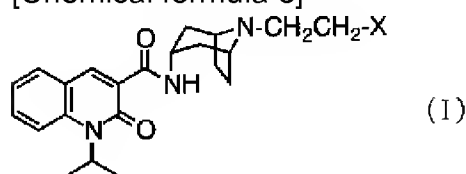
[Problem(s) to be Solved by the Invention]The purpose of this invention is to provide the digestive system disease treating agent based on a new serotonin 4 receptor-stimulation operation.

[0013]

[Means for solving problem]A certain kind of quinoline derivative found out having a strong serotonin 4 receptor-stimulation operation, and this invention persons completed this invention based on the knowledge further, as a result of repeating examination for the compound which has a new serotonin 4 receptor-stimulation operation wholeheartedly.

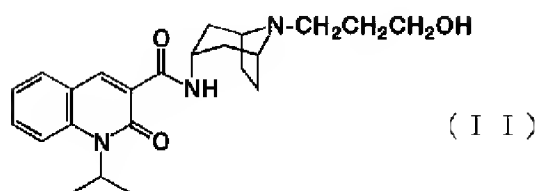
[0014]That is, this invention is a formula. [0015]

[Chemical formula 3]



[0016](X express a hydroxymethyl group, a methoxy group, an ethoxy group, or a morpholino group among a formula.) -- it is a digestive system disease treating agent using the compound expressed or the salt permitted in physic as an active principle. As a compound especially desirable as a digestive system disease treating agent of this invention, it is a formula. [0017]

[Chemical formula 4]



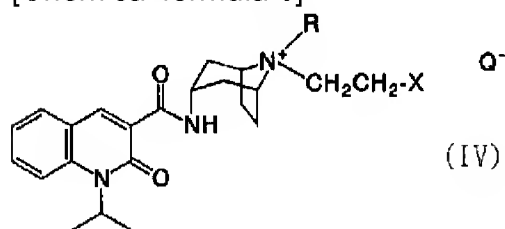
[0018]It is a digestive system disease treating agent coming out and using the compound expressed or the salt permitted in physic as an active principle.

[0019]With the salt of the compound which is an active principle of this invention, for example Hydrochloric acid, hydrobromic acid, Organic acid salt, such as the salt of mineral acids, such as hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, acetic acid, citric acid, tartaric acid, maleic acid, succinic acid, boletic acid, p-toluenesulfonic acid, benzenesulfonic acid, and methanesulfonic acid, is mentioned.

[0020]The compound and formula R-Q (III) which are expressed with formula (I) to the salt furthermore permitted

(R expresses a low-grade alkyl group among a formula, and Q expresses halogen, tosylate, or the mesylate.) -- formula obtained by a reaction with the compound shown [0021]

[Chemical formula 5]



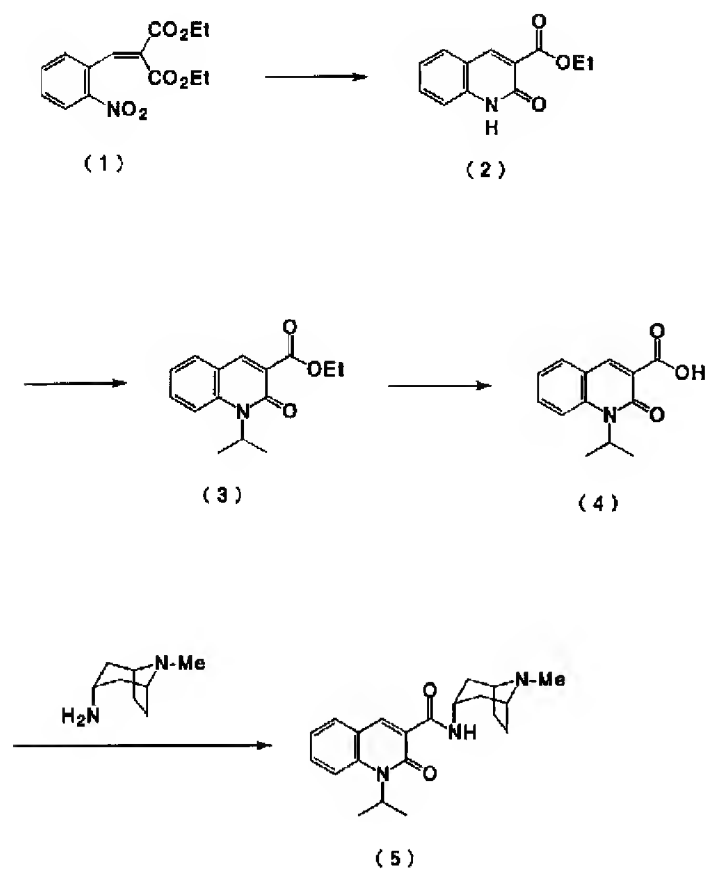
[0022](X, R, and Q are the above and the meaning among a formula.) -- the fourth class salt derivative of the compound expressed can also be mentioned.

[0023]The compound which is an active principle of this invention can be manufactured, for example by the following manufacture scheme I and the manufacture scheme II.

[0024][Manufacture scheme I]

[0025]

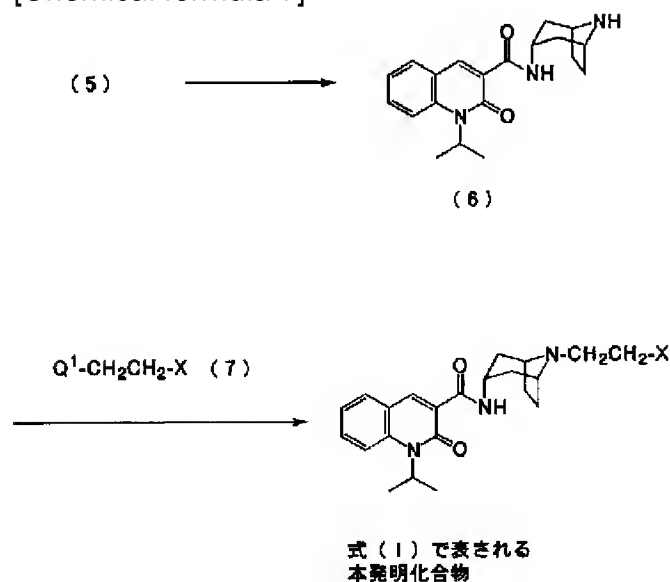
[Chemical formula 6]



[0026][Manufacture scheme II]

[0027]

[Chemical formula 7]



[0028](X are the above and the meaning among a scheme, and Q¹ expresses leaving groups, such as halogen, tosylate, or mesylate.)

In the manufacture scheme I, the compound (1) of a starting material is a journal. OBU

Chemical It can manufacture by the method indicated in SOSAIA tea (J. Chem.Soc., the 3462nd page, 1960).

[0029]The reduction reaction conditions of the usual nitro group may be sufficient as the reductive ring closure reaction from a compound (1) to a compound (2), the ring closure of it can be carried out simultaneously with reduction, and it can obtain a compound (2). reduction reaction conditions -- ** -- the inside of a suitable solvent, palladium carbon, and palladium black. Palladium system catalysts and platinum-carbon, such as palladium barium sulfate and palladium charcoal acid calcium, the catalytic reduction and ** using nickel series catalysts, such as platinum system catalysts, such as platinum black and platinum oxide, and a Raney nickel catalyst, -- there is the reduction method using the reduction and sodium sulfide ammonium chloride using iron or tin among a suitable inert solvent.

[0030]** As a solvent which can be used as a reduction reaction, they are aprotic polar solvents, such as ether, such as hydrocarbons, such as water, acetic acid, alcohols, and hexane, diethylether, and tetrahydrofuran, and N, N dimethylformamide, or those mixed solvents, for example.

[0031]As a solvent which can be used as a reduction reaction of **, they are water, acetic acid, methanol, ethanol, dioxanes, or those mixed solvents, for example.

[0032]** And even the boiling point of 0 ** - a solvent is usually suitable for the reaction temperature of the reduction reaction of **. 30 minutes - 24 hours are usually suitable for the reaction time.

[0033]N-isopropyl-ized reaction for changing into a compound (3) from a compound (2) can be performed on N-alkylation conditions of the usual acid amide group. That is, a compound (2) is made to react to the reactive derivative for introducing an isopropyl group under existence of a base among a suitable solvent. As a reactive derivative for introducing an isopropyl group, it is halogenation isopropyl, such as an isopropyl iodide and isopropyl bromide, for example.

[0034]As a base to be used, for example Alkali metals, such as sodium and potassium, Hydrogenation alkalis, such as sodium hydride and potassium hydride, sodium ethoxide, Alkali alkoxide, such as potassium tertiarybutoxide, sodium hydroxide, They are amines, such as carbonate, such as hydroxylation alkalis, such as potassium hydroxide, sodium carbonate, and potassium carbonate, triethylamine, diisopropylethylamine, pyridine, and N, N dimethylaniline.

[0035]As a solvent to be used, for example Alcohols, such as water, methanol, and ethanol, They are aprotic polar solvents, such as hydrocarbons, such as ether, such as diethylether, dioxane, and tetrahydrofuran, hexane, and benzene, N, N dimethylformamide, and dimethyl sulfoxide, or those mixed solvents.

[0036]Even the boiling point of 0 ** - a solvent is usually suitable for reaction temperature.

[0037]30 minutes - 24 hours are usually suitable for the reaction time.

[0038]The hydrolysis reaction for changing into a compound (4) from a compound (3) can be

performed by the usual hydrolysis condition. For example, it is the alkaline hydrolysis using an acid hydrolysis, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, etc. using hydrochloric acid, hydrobromic acid, hydroiodic acid, acetic acid, sulfuric acid, etc.

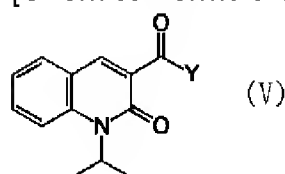
[0039]Even the boiling point of 0 ° - a solvent is usually suitable for reaction temperature.

[0040]30 minutes - 24 hours are usually suitable for the reaction time.

[0041]The amidation reactions for changing into a compound (5) from a compound (4) are a compound (4) or its reactive derivative, and the end 3-amino- 8. - Methyl-8-azabicyclo octane [3.2.1]] [journal OBU American chemical SOSAIA tea The 79th volume, The 4194th page and 1957] can be made to be able to react and it can manufacture.

[0042]As a compound (4) or its reactive derivative, it is a formula. [0043]

[Chemical formula 8]



[0044](Y expresses a hydroxyl group, a halogen atom, an alkoxy group, an allyloxy group, alkoxy carbonyloxy group, an acyloxy group, an imidazolyl group, and an azido group among a formula.) -- it is a compound expressed.

[0045]Y -- concrete -- a hydroxyl group, chlorine, and bromine -- it needs -- halogen atoms, such as base, and methoxy. The alkoxy group of which ethoxy carbon numbers 1-6, phenoxy, p-nitrophenoxy, Allyloxy groups, such as substitution, such as pentachloro phenoxy, or unsubstituted phenyloxy, They are an acyloxy group of the carbon numbers 2-7, such as alkoxy carbonyloxy group of the carbon numbers 1-6, such as ethoxycarbonyloxy, t-butyl carbonyloxy, and benzoyloxy one, an imidazolyl group, and an azido group.

[0046]The compound (4) denoted by formula (V) or its reactive derivative can be manufactured, for example by the following method.

[0047]In the case of the reactive derivative whose Y is a halogen atom, it can obtain by making a compound (4) react to halogenating agents, such as oxalyl chloride, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, and phosphorus tribromide.

[0048]As a solvent, dichloromethane, dichloroethane, chloroform, benzene, toluene, tetrahydrofuran, N, N dimethylformamide, etc. can be used. Even the boiling point of -20 ° - a solvent is suitable for reaction temperature.

[0049]In the case of the reactive derivative whose Y is an alkoxy group, they are a compound (4) and formula R¹-OH (VI).

(R¹ expresses an alkyl group among a formula.) -- it can obtain by making the alcohol

expressed react.

[0050]The case among a suitable solvent can perform a reaction with a non-solvent. When using a solvent, toluene, xylene, benzene, n-hexane, tetrahydrofuran, N, N dimethylformamide, dimethyl sulfoxide, acetone, dichloromethane, and chloroform can be used, for example. A catalyst may be used, for example, there is a base catalyst of acid catalysts, such as sulfuric acid and p-toluenesulfonic acid, or sodium methoxide, n-butyl lithium, sodium hydride, etc. Even the boiling point of -20 °C - a solvent is suitable for temperature.

[0051]In the case of the reactive derivative whose Y is an alkoxy group, they are a compound (4) and formula R^2-Q^2 (VII).

(R^2 expresses an alkyl group among a formula, and Q^2 expresses chlorine, bromine, iodine, tosylate, or the mesylate.) -- it is -- it can obtain by making it react to sulfate, such as a compound or $R^2_2SO_4$, etc.

[0052]Toluene, xylene, benzene, n-hexane, tetrahydrofuran, dimethyl sulfoxide, N, N dimethylformamide, acetone, and chloroform can be used for the solvent to be used, for example. It is good to perform a reaction under existence of a base preferably. As a base to be used, there are sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, triethylamine, diisopropylethylamine, pyridine, and N, N dimethylaniline, for example. Even the boiling point of -20 °C - a solvent is suitable for temperature.

[0053]In formula (V), the reactive derivative whose Y is an allyloxy group or an acyloxy group can be easily manufactured by using the manufacturing method of activity ester of the usual carvone. Y can also manufacture the reactive derivative which is an alkoxycarbonyl group imidazolyl group or an azido group by adopting the manufacturing method of the mixed acid anhydride of usual carboxylic acid, activity amide, or acid azide, respectively. When Y is an activity or unstable functional group, it is preferred that Y uses it, carboxylic acid (4), i.e., the compound, of isolation which are hydroxyl groups.

[0054]In the manufacture scheme I, the amidation reaction of the reactive derivative of a compound (4) or a compound (4) and end 3-amino-8-methyl-8-azabicyclo [3.2.1] octane can be performed by a publicly known method in itself.

[0055]For example, the reactive derivative of a compound (4), the acid halide denoted by formula (V), With lower alkyl ester or activity ester, imidazolidine, or a mixed acid anhydride, and a method to which 3-amino-8-methyl-8-azabicyclo [3.2.1] octane is made to react, Or the method of combining a compound (4) and end 3-amino-8-methyl-8-azabicyclo [3.2.1] octane directly using a condensing agent can be used.

[0056]When using acid halide, end 3-amino-8-methyl-8-azabicyclo [3.2.1] octane is made to usually react to acid halide even in the boiling point of 0 °C - a solvent under existence of a base or nonexistence among a solvent [inertness / reaction].

[0057]As a solvent, they are ether, tetrahydrofuran, dioxane, a methylene chloride, chloroform, dichloroethane, benzene, toluene, xylene, water, or these mixtures, for example.

[0058]As a base, for example Sodium carbonate, potassium carbonate, sodium hydrogencarbonate, Potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, pyridine, triethylamine, diisopropylethylamine, N, N dimethylaniline, sodium hydride, potassium hydride, and n-butyl lithium can be used.

[0059]30 minutes - 24 hours are usually suitable for the reaction time.

[0060]When making the lower alkyl ester denoted by formula (V), activity ester, imidazolidine or a mixed acid anhydride, and end 3-amino-8-methyl-8-azabicyclo [3.2.1] octane react, the publicly known reaction condition usually used can be adopted.

[0061]When joining together directly using a condensing agent, a compound (4) and end 3-amino-8-methyl-8-azabicyclo [3.2.1] octane are made to usually react even in the boiling point of 0 ° - a solvent under existence of a condensing agent among a solvent [inertness / reaction].

[0062]As a solvent, they are ether, tetrahydrofuran, dioxane, a methylene chloride, chloroform, dichloroethane, benzene, toluene, xylene, water, or these mixtures, for example.

[0063]As a condensing agent, they are dicyclohexylcarbodiimide, carbonyldiimidazole, and 2-chloro-N-methylpyridinium, for example. Iodide, diphenyl phosphoryl azide, diethyl Cyano phosphonate can be used.

[0064]Subsequently, the compound (5) obtained as shown in the manufacture scheme II is demethylated, and it is considered as a compound (6). In this demethylation reaction, it is chloro ethyl. There are a method of using a method, a cyanogen bromide, iodine, N-bromosuccinimide, etc. which use alkyl HAROHORU mates, such as chloro formate, etc., etc.

[0065]A compound (6) and a compound (7) Subsequently, bottom chloroform of existence of a base, The quinoline carboxylic acid derivative of this invention denoted by formula (I) can be obtained by making it react even in the boiling point of 0 ° - a solvent among solvents, such as ethanol, toluene, N, N dimethylformamide, tetrahydrofuran, and dimethyl sulfoxide.

[0066]As a base to be used, there are triethylamine, diisopropylethylamine, N,N-diethylaniline, pyridine, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate, for example.

[0067]

[Mode for carrying out the invention]Although the dose of the compound which is an active principle of this invention changes with symptoms, in 0.01-50 mg / Homo sapiens, and intravenous administration, in internal use, 0.001-10 mg / Homo sapiens is usual, and can usually divide and medicate 1 time per day, or several times per day with the dose on the 1st to an adult.

[0068]The digestive system disease treating agent of this invention can be prepared and used

for solid preparations, such as a tablet, a pill, a capsule, and a granule, or injections, liquids and solutions, an emulsion, a ** agent, etc.

[0069]It can manufacture using the usual additive, for example, an excipient, disintegrator, a binder, lubricant, and a coating substrate by the agitation granulation method, fluidized bed granulation method, and a crushing granulation method to manufacture solid preparations.

[0070]

[Effect of the Invention]this invention compound acts to serotonin 4 acceptor, and has the receptor stimulation operation like serotonin. That is, it has an enterokinesis activation operation and is effective in the therapy of an improvement of digestive symptoms, such as postoperative stomach motility, such as chronic gastritis, diabetes mellitus, and gastric resection, heartburn accompanying a stomach excretory function fall, anorexia, epigastralgia, and abdomen enlarged feeling of, and esophagitis regurgitica, pseudoileus, constipation, etc.

[0071]

[Working example]Hereafter, the example of manufacture, a reference example, an embodiment, and the example of an examination are given, and this invention is explained still more concretely.

[0072]The example 1 of manufacture, and N-. (8-.) (2-hydroxypropyl) The-8-azabicyclo [3.2.1] oct 3-yl-1-isopropyl-2-oxo 1, Manufacture of 2-dihydro-3-quinolinecarboxamide. (1) And N-. (8-azabicyclo [3.2.1] oct 3-yl) A-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamidohydrochloride and the N-(8-methyl-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1, 4.0g of 2-dihydro-3-quinolinecarboxamide, and 1-chloro ethyl Heating flowing back of the 50 ml of 1,2-dichloroethane solution of 1.24 ml of chloro formate was carried out for 1 hour. After distilling off a solvent under a reduced pressure, 40 ml of methanol was added and heating churning was carried out for 1 hour. After distilling off this solvent, silica gel column chromatography (chloroform: NH_3 saturated methanol =20:1) refining was given. It recrystallized from ethyl acetate and the N-(8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamidohydrochloride 2.2g was obtained.

[0073]mp; > 270 **. (2) And N-. (8-.) (3-hydroxypropyl) The-8-azabicyclo [3.2.1] oct 3-yl-1-isopropyl-2-oxo 1, 2-dihydro-3-quinolinecarboxamide and 2.0 g of N-(8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide, 50 ml of ethanol solution of 0.53 ml of 3-bromopropanol and the potassium carbonate 0.81g was stirred at the room temperature for 10 hours. It opened in water, chloroform extracted, the chloroform layer was washed, and it dried with sodium sulfate. The residue produced by distilling off a solvent is given to silica gel column chromatography (chloroform: methanol =20:1) refining, It recrystallized from ethyl acetate and 0.51 g of N-(8-(3-hydroxypropyl)-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide (sample compound 1) was obtained.

[0074]mp; 171-172 ** (ethyl acetate).

[0075]It is made to be the same as that of the example 1 of manufacture except changing 3-bromopropanol of the example 1 of example of manufacture 2 manufacture (2) to a 2-methoxy ethyl bromide. And the N-(8-(2-methoxy ethyl)-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamidohydrochloride (sample compound 2) was obtained.

[0076]mp; 247-249 ** (ethyl acetate).

[0077]It is made to be the same as that of the example 1 of manufacture except changing 3-bromopropanol of the example 1 of example of manufacture 3 manufacture (2) to 2-ethoxyethyl bromide. And N-(8-(2-ethoxyethyl)-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide (sample compound 3) was obtained.

[0078]mp; 99-100 ** (isopropyl ether).

[0079]It is made to be the same as that of the example 1 of manufacture except changing 3-bromopropanol of the example 1 of example of manufacture 4 manufacture (2) to 2-morpholino ethyl bromide. And N-(8-(2-morpholino ethyl)-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide (sample compound 4) was obtained.

[0080]mp; 177-178 ** (ethyl acetate isopropyl ether).

[0081]Manufacture (1)2-oxo 1,2-dihydro-3-quinolinecarboxylic acid [of the reference example 1 and N-(8-methyl-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide] . It is 2-nitrobenzylidenemalononic acid to 700 ml of ethylacetic acid. 53 g of iron powder was agitated [times / several] for 2 hours, having dissolved 45 g of diethyl (J. Org.Chem., the 3462nd page, 1960), and keeping at 80 **.

[0082]After returning to a room temperature, cerite filtration was carried out and filtrate was condensed under the reduced pressure. Silica gel column chromatography (chloroformmethanol =10:1) refining of the obtained oily matter is carried out, and it is 2-oxo 1,2-dihydro-3-quinolinecarboxylic acid. Ethyl 21.3 g was obtained.

[0083]mp: 160-3.2 ** (ethyl acetate).

[0084](2) 1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxylic acid It is 2-oxo 1,2-dihydro-3-quinolinecarboxylic acid to the DMF100ml solution containing the ethylsodium hydride 4.45g. After adding 20 g of ethyl, 31.5 g of iodine isopropyl was added and it agitated at 70 ** for 8 hours. After distilling off DMF under a reduced pressure, residue was opened in water and ethyl acetate extracted. The organic layer was dried with after-washing anhydrous sodium sulfate with water and saturation brine.

[0085]The oily matter obtained by distilling off a solvent under a reduced pressure is given to silica gel column chromatography (ethyl acetate: n-hexane=4:1) refining, and it is 1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxylic acid. 1.55 g of ethyl was obtained.

[0086]mp: 54-7 ** (ethyl acetate).

[0087](3) 1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxylic acid 1-isopropyl-2-oxo 1,2-dihydro-1.55 g of ethyl 3-quinolinecarboxylate, 10 ml of ethanol and a mixed solution of 2 ml of

water containing 0.28 g of sodium hydroxide were agitated overnight [bottom of room temperature]. Separation flush desiccation of the solid which added dilute hydrochloric acid and deposited after distilling off a solvent is carried out, and it is 1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxylic acid. 0.24 g was obtained.

[0088](4) And N-(8-methyl-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3- [0.5 g of quinolinecarboxamide 1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxylic acid] Flowing-back churning of the included 5 ml of thionyl chloride solution was carried out for 2 hours. After fully distilling off thionyl chloride under a reduced pressure, 3 ml of benzene was added. And it was dropped into a benzene solution of the above-mentioned acid chloride under ice-cooling of 3 ml of benzene solution containing 0.36 g of 3-amino-8-methyl-8-azabicyclo [3.2.1] octane, and agitated at a room temperature for 2 hours. After adding ethyl acetate, water and saturated sodium bicarbonate water washed an organic layer, and it dried with anhydrous magnesium sulfate. Alumina column chromatography (chloroform) refining of the residue which was able to obtain a solvent after distilling off under a reduced pressure was carried out, and 390 mg of N-(8-methyl-8-azabicyclo [3.2.1] oct 3-yl)-1-isopropyl-2-oxo 1,2-dihydro-3-quinolinecarboxamide was obtained.

[0089]m. p.175.8-177.8 ** (ethyl acetate).

[0090]MS(m/z): 353 (M^+), 214, 172, 84.

[0091]IRnu(cm^{-1} , Neat): 3263, 1673, 1528, 1206.

[0092]NMR(ppm, CDCl_3): 1.68 (6H, d, $J=7.2$ Hz), 1.76 (1H, s), 1.83 (1H, s), 2.00-2.40 (6H, m), 2.34 (3H, s), 3.10-3.28 (2H, m), 4.30 (1H, q, $J=7.2$ Hz), 5.40-5.90 (1H, m), 7.22-7.33 (1H, m), 7.55-7.70 (2H, m), 7.75 (1H, d, $J=7.8$ Hz), 8.83 (1H, s), 10.48 (1H, d, $J=7.2$ Hz).

Embodiment 1 formula (inside of 1 dose)

A 10 mg compound (sample compound 1) of the example 1 of manufacture. Lactose 50 mg
Cornstarch 59.75 mg. Crystalline cellulose 27mg carmellose calcium 27mg
hydroxypropylcellulose 5.25mg magnesium stearate 1 mg. [a compound of the example 1 of
sum total 180-mg manufacture, lactose, cornstarch, crystalline cellulose and carmellose
calcium] It mixed uniformly and a hydroxypropylcellulose aqueous solution was added 10% to
this, and after kneading, it dried, screening of the granulation was carried out by 30M screen, it
was considered as uniform granulation, magnesium stearate was added and tableted, and it
was considered as a tablet.

[0093]Embodiment 2 formula (inside of 1 dose)

The 10 mg compound (sample compound 1) of the example 1 of manufacture. Lactose . 50 mg
Cornstarch 59.75-mg crystalline cellulose . 27mg carmellose calcium 27mg
hydroxypropylcellulose 5.25mg magnesium stearate 1 mg of the compound of the example 1
of sum total 180-mg manufacture, lactose, cornstarch, crystalline cellulose, and carmellose
calcium are mixed uniformly, The hydroxypropylcellulose ethanol solution was added 10% to

this, after kneading, it dried, screening of the granulation was carried out by 30M screen, it was considered as uniform granulation, magnesium stearate was added and tableted, and it was considered as the tablet.

[0094]Embodiment 3 formula (inside of 1 dose)

The 1 mg compound (sample compound 1) of the example 1 of manufacture. Lactose . 59 mg Cornstarch 59.75-mg crystalline cellulose . 27mg carmellose calcium 27mg hydroxypropylcellulose 5.25mg magnesium stearate 1 mg of the compound of the example 1 of sum total 180-mg manufacture, lactose, cornstarch, crystalline cellulose, and carmellose calcium are mixed uniformly, The hydroxypropylcellulose aqueous solution was added 10% to this, after kneading, it dried, screening of the granulation was carried out by 30M screen, it was considered as uniform granulation, magnesium stearate was added and tableted, and it was considered as the tablet.

[0095]Embodiment 4 formula (inside of 1 dose)

The 0.1 mg compound (sample compound 1) of the example 1 of manufacture. Lactose 59.9 mg Cornstarch 59.75 mg. Crystalline cellulose 27mg carmellose calcium 27mg hydroxypropylcellulose 5.25mg magnesium stearate 1 mg. [the compound of the example 1 of sum total 180-mg manufacture, lactose, cornstarch, crystalline cellulose, and carmellose calcium] It mixed uniformly and the hydroxypropylcellulose aqueous solution was added 10% to this, and after kneading, it dried, screening of the granulation was carried out by 30M screen, it was considered as uniform granulation, magnesium stearate was added and tableted, and it was considered as the tablet.

[0096]Example of examination 1. serotonin 4 (5-HT₄) receptor-stimulation operation Section animal; the Hartley system guinea pig maleness (250-400g)

The Section method; the longitudinal muscle acquired from the intestinum ileum of the juxtaposition 10 - 20 cm was used for the experiment from the ileocecum from the Hartley system guinea pig. The sample of the longitudinal muscle hung in Krebs solution (32-34 **), covered the load of about 0.8 g, and aerated O₂ and 5%CO₂ 95%. The reaction was measured in ****. Voltage was made low and after giving the electrical stimulation for 1 millisecond for about 2 to 3 hours and stabilizing it by frequency 0.2 Hz, was stabilized for about 1 hour. After checking that electrical stimulation contraction is reinforced by 5-HT of the concentration of 10⁻⁸M, it experimented about the operation of a sample. Since he was excused from the sample at least for 45 minutes, addition of the sample was performed cumulatively.

[0097]<Reference-documents> Craig, D. A. and Clarke D. E.: Pharmacological characterization of a neuronal receptor for 5-hydroxytryptamine in guinea pig ileum with. properties similar to. the 5-hydroxytryptamine₄ receptor:The Journal of Pharmacology and

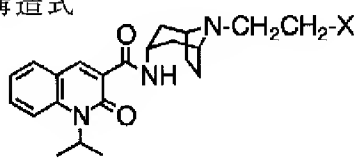

Experimental Therapeutics 252: 1378-1386, 1990.

[0098]Section sample; a sample and cisapride (cisapride) were dissolved and diluted in distilled water or DMSO. A sample was prepared and applied so that concentration of DMSO in Bath might be 0.3% or less.

[0099]A constitutional formula of each sample is shown in the following table 1-.

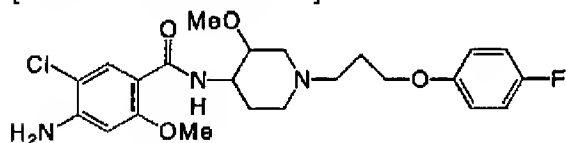
[0100]

[Table 1]

構造式	
	
検体	X
1	CH ₂ OH
2	OMe
3	OEt
4	

[0101]The control sample 1; cisapride [0102]

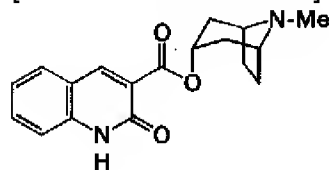
[Chemical formula 16]



[0103]A compound given in the control sample 2;US patent 5th and the No. 106851

Description [0104]

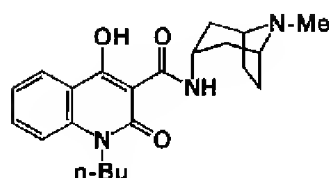
[Chemical formula 17]



[0105]Control sample 3; a compound given in the European Patent 0458636A No. 1

Description [0106]

[Chemical formula 18]



[0107]The maximum contraction quantity by the calculating method sample of Section result was made into 100%, and it asked for the concentration (EC50) from which electrical stimulation contraction potentiation will be 50%.

[0108]Analyzing method: RS1 (BBN software product company) was used.

[0109]Section result ; A result is shown in Table 2.

[0110]

[Table 2]

検体番号	ED50 (nM)
1	32.0
2	15.0
3	18.7
4	25.5
対照 1	271.3
2	> 3000
3	> 3000

[0111]The example of examination 2.5-HT₄ receptor binding depressant action Section method;

1. Preparation of film preparation (5-HT₄ receptor)

1) Extract guinea pig striatum guinea pig (Hartley system, **, CHARUZU libber) striatum, and it is 20. Homogenize with 50 mM HEPESU buffer solution (pH 7.4) of a fold amount, and 48,000 G (27,000 rpm), Carry out the at-long-intervals heart for 10 minutes, and. [dregs] 37 ** and 30 after being suspended again After that [.] which performed the incubation between parts, the at-long-intervals heart was carried out by 27,000 rpm for 10 minutes, it was suspended with pargyline 10⁻⁶M and the HEPESU buffer solution of 0.1% ascorbic acid content, and dregs were used for binding experiments.

[0112]2) homogenizing a guinea pig intestinum-ileum longitudinal muscle guinea pig intestinum-ileum longitudinal muscle with a Teflon glass homogenizer by 0.32 M sucrose, and removing an upside lipid layer and dregs after 900 G and the 10-minute heart at long intervals

-- supernatant liquid -- 100,000 G (48,000 rpm) -- centrifugality was carried out for 1 hour. .
 [dregs] It is again suspended in mM HEPESU buffer solution, and 50 37. ** and 30 After performing the incubation between parts, the at-long-intervals heart was carried out by 48,000 rpm for 20 minutes, it was suspended with the HEPESU buffer solution of pargyline 10^{-6} M and 0.1 %ascorbic acid content, and dregs were used for binding experiments.

[0113]a 2.5-HT₄ receptor attachment inhibition experiment film preparation -- [³H] GR113808 (0.1 nM) (Amersham) and a sample -- last capacity 1.0 ml -- a part for 25 ** and 30 -- between -- an incubation -- it carried out. The coupling amount obtained under 5-HT (3×10^{-5} M) existence was made into the nonspecific coupling amount. The harvester performed B/F separation with the GF/B filter which carried out 0.1 % polyethyleneimine treatment, and washing was made into 1 time.

[0114]Section sample; the tested drug dissolved into DMSO and the last concentration examined it in DMSO 1%.

[0115]A calculating method of Section result; the IC₅₀ value of the drug in a coupling inhibition experiment was calculated according to the program of IC₅₀ in Windows-origin (micro cull software company).

[0116]Section result; a result is shown in Table 3.

[0117]

[Table 3]

検体番号	回腸 (n = 3) IC ₅₀ (nM)
1	42.19 ± 6.29
2	78.50 ± 14.63
3	68.70 ± 7.32
4	78.14 ± 14.52
シサプリド	97.47 ± 9.17

[0118]The example of examination 3. receptor preference Section method;

1) The compatibility to a D₂ receptor D₂ acceptor is [³H] to a rat striatum film. The raclopride (Daiichi Pure Chemicals Co., Ltd.) coupling inhibition operation examined. Rat striatum was homogenized with 50mM tris hydrochloric acid buffer solution (pH 7.4), and it centrifuged by 48,000 G. The tris hydrochloric acid buffer solution washed sediment once. It was suspended in 50mM tris hydrochloric acid buffer solution (pH 7.4 containing 120mM NaCl, 5mM KCl, 2mM

CaCl₂, and 1mM MgCl₂), and sediment was made into the film preparation. It is 1nM [³H] about a film preparation (0.5-mg protein / ml). It was made to react to raclopride for 60 minutes at 25 °C.

[0119]The film was captured after the end of a reaction using the harvester. Nonspecific binding was considered as binding under 10microM haloperidol existence.

[0120]2) The [³H] GR65630 (Daiichi Pure Chemicals Co., Ltd.) coupling-inhibition operation to a rat cerebral-cortex film examined the compatibility to the 5-HT₃ receptor 5-HT₃ acceptor. The rat cerebral cortex was homogenized with 50mM HEPESU buffer solution (pH 7.4), and it centrifuged by 48,000 G. The HEPESU buffer solution washed sediment once. It was suspended in 50mM HEPESU buffer solution, and sediment was made into the film preparation. The film preparation was made to react to 0.2nM[³H] GR65630 for 30 minutes at 37 °C.

[0121]The film was captured after the end of a reaction using the harvester. Nonspecific binding was considered as binding under 1microM ZAKOPURADO existence.

[0122]3) The [³H]8-OH-DPAT (Daiichi Pure Chemicals Co., Ltd.) coupling inhibition in a guinea pig cerebral-cortex film examined the compatibility to the 5-HT_{1A} receptor 5-HT_{1A} receptor.

The guinea pig cerebral cortex was homogenized with 50mM tris hydrochloric acid buffer solution (pH 7.7), and it centrifuged by 48,000 G. The tris hydrochloric acid buffer solution washed sediment once. It was suspended in 50mM tris hydrochloric acid buffer solution (pH 7.7 which contains AsH₂ 0.1% 0.01 mM pargyline), and sediment was made into the film preparation. The film preparation was made to react to 1nM[³H]8-OH-DPAT for 15 minutes at 37 °C.

[0123]The film was captured after the end of a reaction using the harvester. Nonspecific binding was considered as binding under 10microM and 5-HT existence.

[0124]The <Reference documents> GROSSMAN and C.J., KILPATRICK, G.J. & BUNCE, and KT. (1993) Development of. aradioligand binding assay for 5-HT₄receptors in guinea-pig and rat brain. Br.J.Pharmacol., 109,618-624.

[0125]Section sample; the tested drug dissolved into DMSO and the last concentration examined it in DMSO 1%.

[0126]A calculating method of Section result; the IC₅₀ value of the drug in a coupling inhibition experiment was calculated according to the program of IC₅₀ in Windows-origin.

[0127]Section result;

[0128]

[Table 4]

検体番号	1	2	3	4	シサプリド
ドーパミンD2受容体拮抗作用 (IC ₅₀ , nM)	—	—	—	—	107.5
5-HT ₃ 受容体拮抗作用 (IC ₅₀ , nM)	977	811	423	509	97.7
5-HT _{1A} 受容体拮抗作用 (IC ₅₀ , nM)	—	—	—	—	64.7

— : 10 μ Mで作用なし

[0129]Example of examination 4. enterokinesis promotion operation (term a dog and after a meal)

Section animal; -- female beagle Section method; -- the experiment conducted creation and an experiment of the model dog by referring to Hitoshi Yoshida's method.

[0130][force transducer (the sensor for contractile force measurement; Star Medical F-12IS)] After making an incision in the abdomen, after anesthetization by pentobarbital (30mg [kg] /, i.v.) Antrum of stomach (it is 3 cm from the pylorus wheel part to the mouth side), It sewed on five places of the duodenum (it is 5 cm from the pylorus wheel part to the anus side), the jejunum (it is 70 cm from the pylorus wheel part to the anus side), an intestinum-ileum terminal part (it is 5 cm from the time colon joined part to the mouth side), and the colon (it is 5 cm from a time colon joined part to the regio analis). The lead of the force transducer was taken out from the flank to the back through hypodermic, and connected the connector. After the operation and a dog were dressed with the protection jacket, and the connector was stored in this. The enterokinesis was measured from two weeks after the operation. In order to perform measurement by no restraining, the telemeter (electric wave type data transmitter; Star Medical DAT-80T) was connected to the connector, and contraction movement of each part of an alimentary canal was measured. Data was downloaded to the computer (PC9801FA by NEC Corp.) via the telemeter (receiver; Star Medical DAT-80A), and conducted preservation and analysis.

[0131]Administration of the drug (vehicle, cisapride, and sample 5) performed intravenous administration from the forelimb, 2 hours after giving food (1116 kcal; made by an oriental yeast company).

[0132]<Reference-documents> Yoshida. N. and Ito. T. : AS-4370, a new gastrokinetic agent,enhances upper gastrointestinal motor activity in conscious dogs :TheJournal of Pharmacology and Experimental Therapeutics 257781-787, 1991. Section sample; Cisapride

and the sample 5 dissolved in 0.5% of dl-lactic acid solution. Vehicle was taken as 0.5% of dl-lactic acid solution.

[0133]A calculating method of Section result; movement of the alimentary canal was computed by computer every 15 minutes as motility index (g-min (M. I.)). (Momentum computed the area of the portion surrounded with the contraction wave form drawn on the screen by computer, and the ground line.) Analysis software; Star Medical soft organ kinematic analysis soft ESC-820 antrum of stomach, The duodenum. and after-administration 0 - the 15-minute average of a promotion operation [in / (total of M.I. (%) of 0 - 1 hour), / the 15 minute average of the promotion operation in after-administration 0 to 1 hour / , i.e.,/4 show the jejunum, and / colon / the intestinum ileum and / 0.5 hour] -- that is. (Total of M.I. (%) of 0 - 0.5 hour) / 2 showed. M.I. at this time (%) is computing the average as 100% for front [administration] 15/30 minute.

[0134]Section result; a result is shown in drawing 1.

[0135]Example of examination 5 The toxicity at the time of administering [kg] orally for 1 time per and 14 days day in 75,150 of the sample compound 1 of the example 1 of manufacture and 300mg /was examined using the Wistar system rat (one groups [seven]) of a 14 days of rat repetition internal use toxicity test 5-week old sex. Observation and measurement of body weight of general status were performed during the dosing period, and it carried out blood and a blood chemistry inspection, a urinalysis, organ weight measurement, biopsy, etc. at the time of the end of administration.

[0136]As a result, a loss weight and increase inhibition were seen by a 300mg [/kg] group, and two examples of a male presented tremor, a spasm, etc. and died. By kg, the increase in transformer amylase activities was accepted in 300mg /of female not less than 150mg [kg] /and male. No observed adverse effect level was presumed in 75mg/kg, and when the amount of drug effect was taken into consideration, toxicity was imagined to be a weak thing.

[Translation done.]